



3-methylglutaconyl-CoA hydratase deficiency

3-methylglutaconyl-CoA hydratase deficiency is an inherited condition that causes neurological problems. Beginning in infancy to early childhood, children with this condition often have delayed development of mental and motor skills (psychomotor delay), speech delay, involuntary muscle cramping (dystonia), and spasms and weakness of the arms and legs (spastic quadriparesis). Affected individuals can also have optic atrophy, which is the degeneration (atrophy) of nerve cells that carry visual information from the eyes to the brain.

In some cases, signs and symptoms of 3-methylglutaconyl-CoA hydratase deficiency begin in adulthood, often in a person's twenties or thirties. These individuals have damage to a type of brain tissue called white matter (leukoencephalopathy), which likely contributes to progressive problems with speech (dysarthria), difficulty coordinating movements (ataxia), stiffness (spasticity), optic atrophy, and a decline in intellectual function (dementia).

Affected individuals who show symptoms of 3-methylglutaconyl-CoA hydratase deficiency in childhood often go on to develop leukoencephalopathy and other neurological problems in adulthood.

All people with 3-methylglutaconyl-CoA hydratase deficiency accumulate large amounts of a substance called 3-methylglutaconic acid in their body fluids. As a result, they have elevated levels of acid in their blood (metabolic acidosis) and excrete large amounts of acid in their urine (aciduria). 3-methylglutaconyl-CoA hydratase deficiency is one of a group of metabolic disorders that can be diagnosed by the presence of increased levels 3-methylglutaconic acid in urine (3-methylglutaconic aciduria). People with 3-methylglutaconyl-CoA hydratase deficiency also have high urine levels of another acid called 3-methylglutaric acid.

Frequency

3-methylglutaconyl-CoA hydratase deficiency is a rare disorder; at least 20 cases have been reported in the scientific literature.

Genetic Changes

Mutations in the *AUH* gene cause 3-methylglutaconyl-CoA hydratase deficiency. This gene provides instructions for producing 3-methylglutaconyl-CoA hydratase, an enzyme that is involved in breaking down a protein building block (amino acid) called leucine to provide energy for cells. This amino acid is broken down in cell structures called mitochondria, which convert energy from food into a form that cells can use.

AUH gene mutations lead to an absence of enzyme activity. Without any functional 3-methylglutaconyl-CoA hydratase, leucine is not properly broken down, which leads to a buildup of related compounds, including multiple acids: 3-methylglutaconic acid, 3-methylglutaric acid, and 3-hydroxyisovaleric acid. Researchers speculate that an accumulation of these acids in the fluid that surrounds and protects the brain and spinal cord (the cerebrospinal fluid or CSF) can damage these structures and contribute to the neurological features of 3-methylglutaconyl-CoA hydratase deficiency.

Because the age at which the condition begins varies widely and because the signs and symptoms improve in some affected children, researchers speculate that other genes or environmental factors may play a role in the features of 3-methylglutaconyl-CoA hydratase deficiency.

Inheritance Pattern

This condition is inherited in an autosomal recessive pattern, which means both copies of the gene in each cell have mutations. The parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but they typically do not show signs and symptoms of the condition.

Other Names for This Condition

- 3-methylglutaconic aciduria, type I
- 3-MG-CoA-hydratase deficiency
- AUH defect
- MGA, type I
- MGA1
- MGCA1
- primary 3-methylglutaconic aciduria

Diagnosis & Management

These resources address the diagnosis or management of 3-methylglutaconyl-CoA hydratase deficiency:

- Baby's First Test
<http://www.babysfirsttest.org/newborn-screening/conditions/3-methylglutaconic-aciduria>
- Genetic Testing Registry: 3-Methylglutaconic aciduria
<https://www.ncbi.nlm.nih.gov/gtr/conditions/C0342727/>
- MedlinePlus Encyclopedia: Metabolic Acidosis
<https://medlineplus.gov/ency/article/000335.htm>

These resources from MedlinePlus offer information about the diagnosis and management of various health conditions:

- Diagnostic Tests
<https://medlineplus.gov/diagnostictests.html>
- Drug Therapy
<https://medlineplus.gov/drugtherapy.html>
- Surgery and Rehabilitation
<https://medlineplus.gov/surgeryandrehabilitation.html>
- Genetic Counseling
<https://medlineplus.gov/geneticcounseling.html>
- Palliative Care
<https://medlineplus.gov/palliativecare.html>

Additional Information & Resources

MedlinePlus

- Encyclopedia: Metabolic Acidosis
<https://medlineplus.gov/ency/article/000335.htm>
- Health Topic: Amino Acid Metabolism Disorders
<https://medlineplus.gov/aminoacidmetabolismdisorders.html>
- Health Topic: Genetic Brain Disorders
<https://medlineplus.gov/geneticbraindisorders.html>
- Health Topic: Movement Disorders
<https://medlineplus.gov/movementdisorders.html>
- Health Topic: Newborn Screening
<https://medlineplus.gov/newbornscreening.html>

Genetic and Rare Diseases Information Center

- 3-methylglutaconyl-CoA hydratase deficiency (AUH defect)
<https://rarediseases.info.nih.gov/diseases/10321/3-methylglutaconyl-coa-hydratase-deficiency-auh-defect>

Educational Resources

- Centers for Disease Control and Prevention: Facts About Developmental Disabilities
<https://www.cdc.gov/ncbddd/developmentaldisabilities/facts.html>
- Cleveland Clinic: Dementia
<http://my.clevelandclinic.org/health/articles/types-of-dementia>

- Disease InfoSearch: 3-Methylglutaconic aciduria
<http://www.diseaseinfosearch.org/3-Methylglutaconic+aciduria/7606>
- KidsHealth from Nemours: Delayed Speech or Language Development
<http://kidshealth.org/en/parents/not-talk.html>
- MalaCards: 3-methylglutaconic aciduria, type i
http://www.malacards.org/card/3_methylglutaconic_aciduria_type_i_2
- Merck Manual Home Edition for Patients and Caregivers: Acidosis
<http://www.merckmanuals.com/home/hormonal-and-metabolic-disorders/acid-base-balance/acidosis>
- Orphanet: 3-methylglutaconic aciduria type 1
http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=67046

Patient Support and Advocacy Resources

- CLIMB: Children Living with Inherited Metabolic Diseases (UK)
<http://www.climb.org.uk/>
- Organic Acidemia Association
<http://www.oaanews.org/mga.html>

Genetic Testing Registry

- 3-Methylglutaconic aciduria
<https://www.ncbi.nlm.nih.gov/gtr/conditions/C0342727/>

ACT Sheets

- Elevated C5-OH Acylcarnitine
<https://www.ncbi.nlm.nih.gov/books/NBK55827/bin/C5-OH.pdf>

Scientific Articles on PubMed

- PubMed
<https://www.ncbi.nlm.nih.gov/pubmed?term=%28%283-methylglutaconyl-coa+hydratase+deficiency%5BTIAB%5D%29+OR+%283-methylglutaconic+aciduria+type+I%5BTIAB%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+3600+days%22%5Bdp%5D>

OMIM

- 3-METHYLGLUTACONIC ACIDURIA, TYPE I
<http://omim.org/entry/250950>

Sources for This Summary

- Eriguchi M, Mizuta H, Kurohara K, Kosugi M, Yakushiji Y, Okada R, Yukitake M, Hasegawa Y, Yamaguchi S, Kuroda Y. 3-Methylglutaconic aciduria type I causes leukoencephalopathy of adult onset. *Neurology*. 2006 Nov 28;67(10):1895-6.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/17130438>
- IJlst L, Loupatty FJ, Ruiter JP, Duran M, Lehnert W, Wanders RJ. 3-Methylglutaconic aciduria type I is caused by mutations in AUH. *Am J Hum Genet*. 2002 Dec;71(6):1463-6. Epub 2002 Nov 14. Erratum in: *Am J Hum Genet*. 2003 Sep;73(3):709.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/12434311>
Free article on PubMed Central: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC378594/>
- Mercimek-Mahmutoglu S, Tucker T, Casey B. Phenotypic heterogeneity in two siblings with 3-methylglutaconic aciduria type I caused by a novel intragenic deletion. *Mol Genet Metab*. 2011 Nov;104(3):410-3. doi: 10.1016/j.ymgme.2011.07.021. Epub 2011 Jul 26.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/21840233>
- Wortmann SB, Duran M, Anikster Y, Barth PG, Sperl W, Zschocke J, Morava E, Wevers RA. Inborn errors of metabolism with 3-methylglutaconic aciduria as discriminative feature: proper classification and nomenclature. *J Inherit Metab Dis*. 2013 Nov;36(6):923-8. doi: 10.1007/s10545-012-9580-0. Epub 2013 Jan 8. Review.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/23296368>
- Wortmann SB, Kluijtmans LA, Engelke UF, Wevers RA, Morava E. The 3-methylglutaconic acidurias: what's new? *J Inherit Metab Dis*. 2012 Jan;35(1):13-22. doi: 10.1007/s10545-010-9210-7. Epub 2010 Sep 30. Review.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/20882351>
Free article on PubMed Central: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3249181/>
- Wortmann SB, Kluijtmans LA, Rodenburg RJ, Sass JO, Nouws J, van Kaauwen EP, Kleefstra T, Tranebjaerg L, de Vries MC, Isohanni P, Walter K, Alkuraya FS, Smuts I, Reinecke CJ, van der Westhuizen FH, Thorburn D, Smeitink JA, Morava E, Wevers RA. 3-Methylglutaconic aciduria--lessons from 50 genes and 977 patients. *J Inherit Metab Dis*. 2013 Nov;36(6):913-21. doi: 10.1007/s10545-012-9579-6. Epub 2013 Jan 25.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/23355087>
- Wortmann SB, Kremer BH, Graham A, Willemsen MA, Loupatty FJ, Hogg SL, Engelke UF, Kluijtmans LA, Wanders RJ, Illsinger S, Wilcken B, Cruysberg JR, Das AM, Morava E, Wevers RA. 3-Methylglutaconic aciduria type I redefined: a syndrome with late-onset leukoencephalopathy. *Neurology*. 2010 Sep 21;75(12):1079-83. doi: 10.1212/WNL.0b013e3181f39a8a.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/20855850>

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